

Amendments to the Specification

- (1) Replace the paragraph on page 4, line 28 to page 5, line 7 with the following paragraph:

C¹

Mutations can first be identified by comparison to sequences present in public databases for human mitochondrial DNA, *e.g.*, at <http://www.gen.emory.edu/mitomap.html> the URL address: http file type, www host server, gen.emory.edu domain name, mitomap.html directory. Any single basepair substitution identified in the sample DNA compared to a normal sequence from a database can be confirmed as being a somatic mutation as opposed to a polymorphic variant by comparing the sample mitochondrial DNA or sequences obtained from it to control cell mitochondrial DNA from the same individual or sequences obtained from it. Control cells are isolated from other apparently normal tissues, *i.e.*, tissues which are phenotypically normal and devoid of any visible, histological, or immunological characteristics of cancer tissue. A difference between the sample and the control identifies a somatic mutation which is associated with the tumor.

- (2) Replace the paragraph on page 5, lines 8-24 with the following paragraph:

C²

An alternative to serially sequencing the entire mitochondrial genome in order to identify a single basepair substitution is to use hybridization of the mitochondrial DNA to an array of oligonucleotides. Hybridization techniques are available in the art which can rapidly identify mutations by comparing the hybridization of the sample to matched and mismatched sequences which are based on the human mitochondrial genome. Such an array can be as simple as two oligonucleotide probes, one of whose sequence matches the wild-type or mutant region containing the single base substitution (matched probe) and

C2
0004. another whose sequence includes a single mismatched base (mismatch control probe). If the sample DNA hybridizes to the matched probe but not the mismatched probe, it is identified as having the same sequence as the matched probe. Larger arrays containing thousands of such matched/mismatched pairs of probes on a glass slide or microchip ("microarrays" or "gene chips") are available which are capable of sequencing the entire mitochondrial genome very quickly. Such arrays are commercially available. Review articles describing the use of microarrays in genome and DNA sequence analysis and links to their commercial suppliers are available at ~~www.gene-chips.com~~ the URL address: www host server, gene-chips.com domain name.

(3) Replace the paragraph on page 10, lines 16-22 with the following paragraph:

C3
Sequence analysis. The sequences obtained were first compared to those recorded in the mitochondrial databank at www.gen.emory.edu/mitomap.html the URL address: www host server, gen.emory.edu domain name, mitomap.html directory. Eighty-eight sequence variants were identified (4 - 31 per tumor) that were not recorded in this databank. These included 27 variants which were predicted to alter the amino acid sequence of the encoded protein, 48 variants which were in protein coding regions but predicted to be silent, and 13 which affected rRNA or tRNA genes.
